INTEX

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1. INTRODUCTION [1]

Drugs are rarely administered solely as pure chemical substances, but are almost given as formulated preparations. The principle objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation.

Before a drug substance can be successfully formulated in to a dosage form, many factors must be considered. These factors can be broadly grouped in to three categories.

- Biopharmaceutical considerations (Factors affecting absorption of drugs)
- Drug related factors (Physical and chemical properties of a drug)
- Therapeutic considerations (Disease to be treated and patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc…), the tablet dosage form is the most widely used.

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug .The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills.

Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world**.**

1.1 Tablets

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients.

According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer.

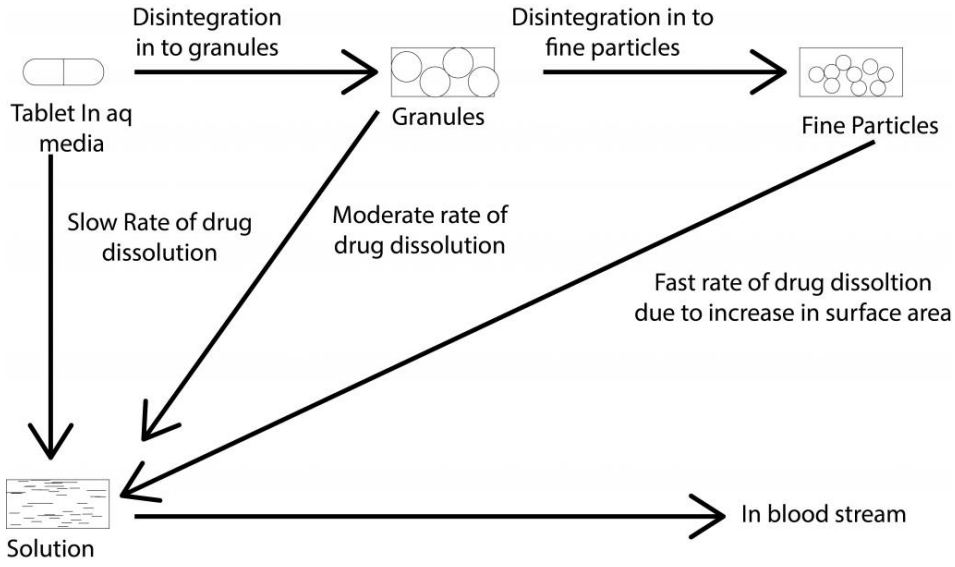


Fig 1.1.Shows schematic flow chart of tablet post administration

They vary greatly in shape, size and weight which depend upon amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics and in other aspects depending upon their intended use and method of

manufacture. Tablets are the most widely used solid dosage form of medicament. Because of their advantages their popularity is continuously increasing day by day.

1.1.1 Advantages [2]

They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

- Cost is lowest of all oral dosage form
- Lighter and compact
- Easiest and cheapest to package and strip
- Easy to swallowing with least tendency for hang-up
- Sustained release product is possible by enteric coating
- Objectionable odour and bitter taste can be masked by coating technique
- Suitable for large scale production
- Greatest chemical and microbial stability over all oral dosage form
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

1.1.2 Disadvantages

In spite of all these advantages, tablet also possesses some disadvantages. The disadvantages of tablets include the following

- Some drugs resist compression in to dense compacts, owing to their amorphous nature or flocculent, low density character.

- Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating.

1.2 CLASSIFICATION OF TABLETS [3]

A. Classification based on mode of administration

- Tablets to be swallowed
- Chewable tablets
- Tablets used in oral cavity
    - Buccal tablets
    - Sublingual tablets
    - Troches and lozenges
    - Dental cones
- Tablets administered other than oral route
    - Implants
    - Vaginal tablets / suppositories

B. Classification based on drug manufacturing process

- Standard compressed tablets
- Multiple compressed tablets
    - Compression-coated tablets
    - Layered tablets
- Coated tablets
- Molded tablets (Tablet triturates)

C. Classification based on drug release profile

- Fast dissolving tablets
- Immediate release tablets
- Controlled Release tablets (Sustained Release Tablets)
- Delayed Release tablets (Enteric coated tablets)

D. Tablets used to prepare solutions

- Effervescent tablets
- Dispersible tablets

1.3 BILAYER TABLETS [4]

Compressed tablets are defined as solid dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

Multilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More are possible

but the design becomes very special. Ideally a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

1.3.1 Advantages of Bilayer tablets

The primary potential advantages of tablets are,

- They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability
- The cost is lower of all oral dosage forms
- They are the lightest and most compact of all
- They are in general the easiest and cheapest to packaging and shipment
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face
- They may provide the greatest case of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid
- They lend themselves to certain special profile products, such as enteric or delayed release products
- They are better suited to large scale production than with other unit oral dosage forms
- They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms

1.3.2 Layer thickness

Layer thickness can be varied within reasonable proportions within the limitations of the tablet press. Thickness is dependent on the fineness of the granulation.

1.3.2.1 Sizes and Shapes

Size is limited by the capacity of the machine with the total thickness being the same as for a single layer tablet. Many shapes other than spherical are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distortion of the layers. Therefore standard concave and flat face beveled edge tooling make for the best appearance, especially when layers are of different colors.

1.3.3 Granulations

For good quality tablets with sharp definition between the layers, special care must be taken as follows,

- Dust fines must be limited. Fines smaller than 100 meshes should be kept as a minimum
- Maximum granule size should be less than 16 meshes for a smooth, uniform scrap off at the die.
- Materials that smear, chalk or coat on the die table must be avoided to obtain clean scrape off and uncontaminated layers.
- Low moisture is essential if incompatibilities are used.
- Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
- Formulation of the multilayer tablets is more demanding than that of single layer tablets for this reason, selection of additives is critical.

1.3.4 Tablet layer press

A tablet multilayer press is simply a tablet press that has been modified so that it has two die filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two layer tablet and a second time for the second layer. Three layer presses are equipped with three such compression cycles.

There are two types of layer presses presently in the use- one in which each layer can be ejected from the press separately for the purpose of weight checking and the second in which the first layer is compressed so hard that the second layer will not bond to it or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper adjustments have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers.

One hazard of layer tablet production is the lack of proper bonding of the layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficient bonded.

In a two layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continuous, gently circulation of the materials through the hoppers and that would otherwise carry over to the second layer and affect layer weight, appearance of the tablet. The same procedure is followed in the three layer press with three hoppers for the three granulations instead of two.

Certain single layer or unit tablet presses are equipped with two pre-compression stations prior to the final compaction. This provides high speed production by increasing dwell time of the

material under pressure making for harder, denser tablets. Eg. Prolonged and immediate release tablet containing penta errythritol tetra nitrate two layer tablets

1.4 FLOATING DRUG DELIVERY SYSTEM [5]

The design of floating drug delivery Systems (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability. Now-a-days most of the pharmaceutical scientist is involved in developing the ideal FDDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release tablet. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract, and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability.

One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.

Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid or effective buoyancy.[6] Floating drug delivery systems are classified depending on the use of two formulation variables, effervescent and non-effervescent systems. [7]

1.4.1 Advantages of floating drug delivery systems

Floating dosage systems form important technological drug delivery systems with gastric retentive behaviour and offer several advantages in drug delivery. These advantages include:

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastroesophageal reflux.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.

1.4.2 Disadvantages of floating drug delivery systems

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

- One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

- These systems also require the presence of food to delay their gastric emptying.

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

- Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed

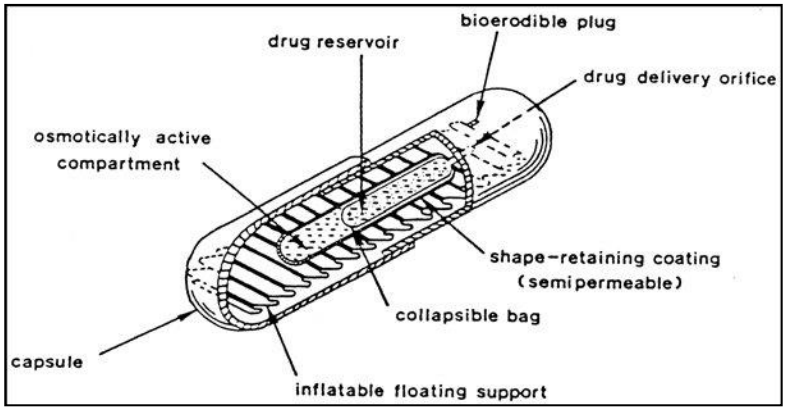
1.4.3 Effervescent system

A drug delivery system can be made to float in the stomach by incorporating a floating chamber which may be filled with vacuum,air or inert gas. The gas in the floating chamber can be introduced either by volatalization of an organic solvent or by the

effervescent reaction between organic acid and bicarbonate salts.

1.4.3.1 Volatile liquid containing system

The gastric retention time of a drug delivery system can be sustained by incorporating floatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasify at body temperature to cause inflation of chamber in the stomach. These devices are osmotically controlled floating system.[8] Intra gastric osmotically controlled drug delivery system consist of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. When the device reaches the stomach, bio erodible capsule quickly disintegrate to release the drug delivery system. The floating supports made up of deformable hollow polymeric bag containing a liquid that gassify at body temperature to inflate the bag. In stomach water is absorbed through the semipermeable membrane into the osmotic compartment to dissolve the salt. An osmotic pressure is thus created, which acts on the collapsible bag, and in turn forces the drug reservoir compartment to reduce it's volume and release the drug solution through the delivery orifice. [9]



Figu 1.2. Osmotically controlled drug delivery system.

1.4.3.2 Gas generating system

These are matrix types of systems prepared with swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastriccontents,CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. A decrease in specific gravity causes the dosage form to float on the chyme.[10] In single unit systems, such as capsules or tablets effervescent substances are incorporated in the hydrophilic polymer and CO_2 bubbles are trapped in the swollen matrix. In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h. In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 hr. Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2.The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of polymer. It is difficult to control in situ acid base reaction and in turn drug release. [11]

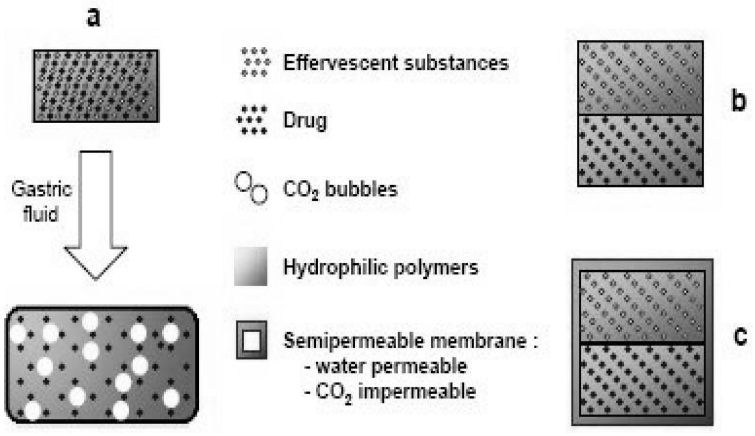


Fig 1.3 Gas generating system: Schematic monolayer drug delivery system(a) Bilayer gas generating system, with (c) or without (b)semipermeable membrane.

1.4.3.3 Raft-forming system

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.[12]

Fig 1.4.Schematic illustration of the barrier formed by a raft-forming system

1.4.4 Non-effervescent floating dosage form

The most commonly used excipients in non-effervescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier.[13]

Hydrodynamically balanced system: On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug. As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air trapped in by swollen polymer maintains density less than unity and confers buoyancy to these dosage forms.

The hydrodynamically balanced system must comply with three major criteria-

- It must have sufficient structure to form cohesive gel barrier
- It must maintain an overall specific density lower than that of gastric content
- It should dissolve slowly enough to serve as reservoir for the delivery system.[10]

The main drawback of HBS is pasivity of operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence on the characteristics and amount of polymer. Effective drug delivery depends upon the balance between drug loading and effect of polymer on it's release profile.[14]

2. LITERATURE REVIEW

- **Yang L et.al,,., [15] (1996)** developed various types of tablets (bilayered and matrix) which are having floating characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methyl cellulose, crospovidone, sodium carboxymethyl cellulose and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a disproportionate 3-layer matrix technology to control drug release.

- **Murata,Y** et.al,,.,**[16] (2000)** developed a floating alginate beds for stomach specific drug delivery were prepared. In this work, two types of alginate gel beds, ALGO (containing vegetable oil) and ALCS (containing chitosan) were prepared, which floated in gastric fluid if they contained a vegetable oil or air in their gel matrix and gradually released the drug metronidazole. The drug-release profile was not affected by the kind of chitosan contained in ALCS. When ALCS containing MZ was administered orally to guinea pigs, it floated on the gastric juice and released the drug into the stomach. Furthermore, the concentration of MZ at the gastric mucosa after administration of ALCS was higher than that in the solution, though the MZ serum concentration was the same regardless of which type of gel was administered. These release properties of alginate gels are applicable not only for sustained release of drugs but also for targetingthe gastric mucosa.

- **Ozdemir et.al,,., [17] (2000)** developed floating bilayer tablets with controlled release for furosemide. This study was designed to enhance the bioavailability of furosemide

by prolonging its duration in the stomach via the floating dosage forms with controlled release. All formulations were prepared as two-layer tablets. The first layer provided floating and contained the mixture of sodium bicarbonate and citric acid to form air bubbles and HPMC K4M as a matrix material to retain the air bubbles. The second layer (release layer) provided controlled release of active material. It contained active material and HPMC K100M as hydrophilic matrix material.

- **Juan Manuel Llabot et.al,.,[18] (2002)** designed the mucoadhesive Bilayered of both immediate release and sustained release tablets of nystatin. The mucoadhesive tablet formulated in this work releases nystatin quickly from the lactose layer and then in a sustained way, during approximately 6 hours, from the polymeric layer. The mixture CB: HPMC 9:1 showed good in vitro mucoadhesion. A swelling-diffusion process modulates the release of nystatin from this layer. A non-Fickian (anomalous) kinetic was observed.

- **Dave B.S et.al,., [19] (2004)** developed a floating drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum and hydroxypropyl methylcellulose were evaluated for gel-forming properties. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated by using full factorial design. The results indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation. No significant difference was observed between the desired release profile and optimized batches. These studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile.

- **S. C. Basak et.al,,[20]** (2004) studied on controlled release HPMC matrix tablets of propanolol Hcl matrix tablets with HPMC polymer to control the release of drug with a view to develop twice daily sustained release dosage form. The resulting matrix tablets prepared with HPMC K4M fulfilled all the official requirements of tablet dosage forms.

- **Pandey H et.al,,., [21] (2005)** developed sustained release bilayer tablet of domperidone using hydrophilic matrix material such as HPMC, carbapol and poly-ethylene oxide. The results indicated that the formulation with HPMC could extend the drug release upto 24hr. All the formulations show diffusion dominated drug release.

- **Muthusamy K, et.al,,.,[22] (2005)** developed preparation and evaluation of lansoprazole floating micropellets were reported·Floating micropellets of 1:1, 1:2 and 1:3 drug to carrier ratios were prepared using HPMC, MC and Chitosan as a carrier. All floating micopellet formulations showed good flow properties except formulation containing HPMC as coating material and packability. Drug loaded micropellets were found to float on simulated gastric fluid and simulated intestinal fluid for more than 12 hour. Drug to chitosan ratio 1:1 showed good incorporation efficiency and high percentage in vitro release of lansoprazole from micropellets.

- **M. Chavanpatil et.al,,., [23]** (2005**)** developed a once-daily sustained release gastro retentive drug delivery system for ofloxacin by using different polymers such as psyllium

husk, hydroxypropyl methylcellulose K100M and crospovidone. In this work HPMC K100M and psyllium husk were used as release retarding agents. Crospovidone was used as swelling agent. The in vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. The high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of ofloxacin. The swelling properties were increased with increasing crospovidone concentration and contributed significantly in drug release from the tablet matrix.

- **Narendra et.al,,.,[24] (2006)** developed an optimized bilayer gastric floating tablet containing metoprolol tartrate using soluble starch for immediate loading dose layer and HPMC was used for sustained release layer with SCMC was used for floating the tablet. Fickian release transport was confirmed as the release mechanism from the optimized formulation. The results demonstrate the feasibility of the model in the development of GFDDS. The results demonstrate the feasibility of the model in the development of GFDDS.

- **Vishnu M Patel G et.al,,.,[25] (2007)** studied the mucoadhesive bilayer tablets of propanolol hydrochloride using the bioadhesive polymers sodium alginate and Carbopol 934P (CP) along with ethyl cellulose as an impermeable backing layer. Tablets containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of in vitro drug release without disintegration in 12 hours. The swelling index was proportional

to Na-alginate content and inversely proportional to CP content. The mechanism of drug release was found to be non-Fickian diffusion and followed zero-order kinetics.

- **Chinam Niranjan Patra et.al,,.,[26] (2007)** developed the bilayered tablets of propanolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethyl cellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. The formulations gave an initial burst effect to provide the loading dose of drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. In vitro dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release.

- **Girish S. Sonara et.al,,.,[27] (2007)** prepared the bilayer and floating - bio adhesive tablets of rosiglitazone maleate. HPMC was used for the sustained release layer and Sodium bicarbonate was used for the floating layer. The floating ability was studied by gamma scintigraphy. The release of rosiglitazone maleate from the tablets followed the matrix first-order release model. The tablet was buoyant for up to 8 h in the human stomach.

- **Multak S et.al,,., [28] (2007**) prepared the once daily sustained release tablets of aceclofenac by direct compression method using HPMC K4M as polymer. Here, the solubility studies of aceclofenac were conducted to select suitable dissolution media. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical, in vitro drug release, stability studies, Preclinical (anti-inflammatory, analgesic, pharmacokinetic and toxicity studies) and clinical

pharmacokinetic studies. Based on the preformulation results, microcrystalline cellulose (MCC), dicalcium phosphate and spray dried lactose (SDL) were selected as directly compressible vehicles. By comparing the dissolution profiles with the marketed product, the tablet containing HPMC (45%) and MCC (30%) along with talc and magnesium stearate (1% w/w, each) (Tablet B7) was considered as a better formulation. This tablet exhibited almost similar drug release profile in different dissolution media as that of marketed tablet. . The composition of this tablet showed almost similar preclinical pharmacological activities and clinic pharmaco kinetic profile as that of marketed tablet composition.

- **Dhake A. S. et.al,,,[29]** (2005) developed sustained release model drug tablet using HPMC in various ratio. The study shows that HPMC is an appropriate polymer that can be used as matrix forming agent prolonged the release of the drug. Preparation of matrices by wet granulation was found to be more effective. Release of drug from the matrices can be adjusted by using release enhancer like lactose and sodium starch glycollate. Drug with HPMC k4m and HPMC E-5 in various proportions like (1:6, 1:5, 1:4) shows the drug release sustained at the rate of 33 mg/hr.

- **Hiremath S. N. et.al,,[30]** (2007) developed sustained release matrix tablet of Metformin Hcl using hydrophilic swellable polymer HPMC with lactose. Three different grade of polymer HPMC K4m, HPMC K100m, HPMC K15m, were used in three different ratios (2:1, 4:1, and 6:1) to retard the drug release from the matrices. Among the three grade of

polymer the tablet prepared with lower viscosity grade (HPMC K4m) shown slightly greater drug release than the higher viscosity grade polymer (HPMC K100, HPMC K15m). So the drug with HPMC K4m ratio of 6:1 shows promising results and released more than 90% drug in 12 hrs.

- **M. Rajesh et.al,, (2010)** [31] were prepared using a hydrophilic polymer Hydroxypropyl methylcellulose K100M (HPMC K100M) with three concentrations (Drug: polymers 1:0.5, 1:0.75 and 1:1) by wet granulation method. Invitro release studies revealed that famotidine formulation with high proportion of HPMC K100M (1:1) was able to sustain the drug release for 10 hours (84.1% ±1.85). Fitting the invitro drug release data to kinetic analysis, all the formulations followed the mechanism of both diffusion and erosion. All the formulations were stored at 45º±2 ºC, 75 ± 5%RH and subjected to stability studies upto 45 days. It showed that all the formulations are physically and chemically stable.
- **Ajay Kumar et.al,, (2013)**[32] were prepared with polymers like HPMC K4M and HPMC K100M using directly compression technique. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, In vitro buoyancy and dissolution studies All the prepared batches showed good In vitro buoyancy. The tablet remained buoyant for 6-10 hours. The tablets with HPMC K100M were found to float for longer duration as compared with formulations containing HPMC K4M. The In vitro dissolution studies confirmed the sustained and non fickian drug release from tablets. Stability studies showed that tablets can be stored at room temperature.
- **Angilicam Avinash et.al,, (2015)**[33] were designed floating tablets to study the influence of different polymers on its release rate. Nine formulations of famotidine containing

varying concentrations of polymers (HPMC E15, HPMC K4M and sodium alginate) were designed The floating matrix tablets of famotidine were prepared by direct compression method. The powder blend was evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausner's ratio; all these values are within the specified limit which indicates good flow properties. The prepared tablets were evaluated for physicochemical parameters such as weight variation, hardness, friability, floating properties (floating lag time, floating time) and drug content. In vitro release studies revealed that out of 9 formulations, formulation F8 was found to be optimized which showed sustain the drug release of 97.11% for 10 hours.

3. AIM AND OBJECTIVE OF PRESENT STUDY

- To design and develop a stable solid oral dosage form of bilayered tablet of aceclofenac with the famotidine in a fixed dose combination to treat Zollinger-Ellison syndrome.

- To select and optimize the concentration of disintegrant for immediate release layer, aceclofenac.

- To optimize the concentration of Polymer for sustaining layer, famotidine.

- To select the dissolution media, by performing solubility studies.

- To evaluate the formulation parameters like weight variation, hardness, friability, disintegration, content uniformity, assay.

- To evaluate the *In-vitro* studies for the prepared trials of bilayered tablets.

- To conduct the accelerated stability studies for the prepared tablets as per ICH guidelines

3.1 PLAN OF WORK

The present work was aimed to carryout for the formulation and evaluation of aceclofenac and famotidine tablets for floating drug delivery system by using polymers such as microcrystalline cellulose, crosspovidone, sodium starch glycolate, lactose, croscarmellose sodium, magnesium stearate, and talc.

This work consists of four steps.

Step 1

- Literature survey
- Selection and collection of drug & raw materials.

Step 2

- Drug-polymer compatibility study by FTIR&DSC.
- Preparation of granules.
- Evaluation of micromeritic properties of granules.
    - Angle of repose
    - Bulk density
    - Tapped density
    - Carr's index
    - Hausner's ratio

Step 3

- Formulation of bilayer floating tablets containing aceclofenac and famotidine drugs.
    - Formulation of immediate release (IR) tablets by direct compression.
    - Formulation of sustain release(SR) tablets by wet granulation.

Step 4

Evaluation of prepared tablets

- Evaluation of prepared Immediate Release tablets
    - Physical appearance
    - Weight variation
    - Thickness
    - Hardness
    - Friability
    - Wetting time
    - Disintegration
    - Dissolution
- Evaluation of Sustained Release tablets.
    - Physical appearance
    - Weight variation
    - Friability
    - Dissolution
    - Swelling index
- Release kinetics
- Stability studies

4.DRUGS AND POLYMER PROFILE

4.1 ACECLOFENAC [34]

Chemical structure

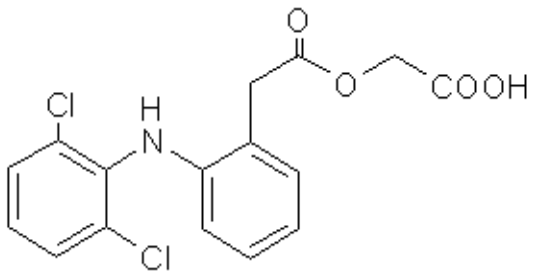


Fig 4.1. Structure of Aceclofenac

IUPAC name

2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid

Chemical formula

$C_{16}H_{13}Cl_2NO_4$

Molecular weight

354.18

Description

Aceclofenac is a white to off-white, odourless crystalline powder

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in alcohol

Melting point

149-153 ºC.

p^{ka} value

4.7

Mechanism of action

Aceclofenac has higher anti-inflammatory action than conventional NSAIDs. It is a cytokine inhibitor. Aceclofenac works by blocking the action of a substance in the body called cyclo-oxygenase. Cyclo-oxygenase is involved in the production of prostaglandins (chemicals in the body) which cause pain, swelling and inflammation. Aceclofenac is the glycolic acid ester of diclofenac.

Pharmacokinetics data of aceclofenac

Oral availability	100%
Bound in plasma	99%
Urinary excretion	70-80%
Volume of distribution	25 -30 L/kg
Half life	3-4 hrs

Side effects

- Gastro intestinal toxicity including abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding (perforation, heart burn, nausea, GI ulcers, vomiting).
- Other events including – abnormal renal function, anemia, dizziness, oedema, elevated liver enzymes, headaches, increased bleeding time, pruritis and rashes.

Drug/Drug Interactions

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyperglycemia may result from the concomitant administration of aceclofenac and ant diabetic drugs, although this is rare. The co administration of aceclofenac with other NSAIDS of corticosteroids may results in increased frequency of adverse event.

Drug/Food Interactions

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (7.99%). The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. Aceclofenac is metabolized to a major metabolite, 4'-hydroxyaceclofenac and to a number of other metabolites including 5-hydroxyaceclofenac, 4'-hydroxydiclofenac, diclofenac and 5-hydroxydiclofenac. Renal excretion is the main route of elimination of aceclofenac with 70

to 80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half-life of the drug is approximately 4 hours.

Uses

It is an analgesic and anti-inflammatory properties, aceclofenac provides symptomatic relief in a variety of painful conditions. Aceclofenac reduces joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis, and is similar in efficacy to ketoprofen, diclofenac, indomethacin and tenoxicam in these patients. Aceclofenac is also effective in other painful conditions (e.g. dental and gynaecological). In contrast to some other NSAIDs, aceclofenac has shown stimulatory effects on cartilage matrix synthesis. Aceclofenac is well tolerated, with most adverse events being minor and reversible, and affecting mainly the GI system.

4.2 FAMOTIDINE [35]

Chemical structure

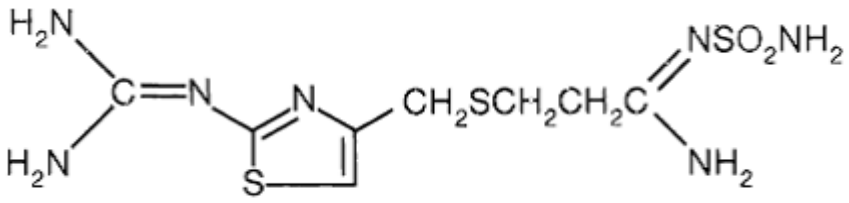


Fig 4.2 Structure of famotidine

IUPAC name

3-([2-(diaminomethyleneamino)thiazol- 4-yl]methylthio)- N'-sulfamoylpropanimidamide.

Chemical formula

$C_8H_{15}N_7O_2S_3$

Molecular weight

337.43.

Description

Famotidine is a white to pale yellow crystalline compound

Solubility

Famotidine is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Melting point

163.5 °C

p^{ka} value

9.29

Mechanism of action/Effect

Famotidine binds competitively to H_2-receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Pharmacokinetics of famotidine

Oral availability	Ranges from 40 to 50%,
Bound in plasma	15 to 22%
Urinary excretion	Approximately 65-80% of an IV dose is excreted unchanged
Volume of distribution	1.0 to 1.3 L/kg
Half life	2 to 4 hrs

Side effects

Side-effects are associated with famotidine use. In clinical trials, the most common adverse effects were headache, dizziness, and constipation or diarrhea. Antacid preparations such as famotidine, by suppressing acid-mediated breakdown of proteins, lead to an elevated risk of developing food or drug allergies. This happens due to undigested proteins then passing into the gastrointestinal tract where sensitization occurs. It is unclear whether this risk occurs with only long-term use or with short-term use as well.

Drug/Drug Interactions

Famotidine, like other drugs that reduce stomach acid, may interfere with the absorption of drugs that require acid for adequate absorption. Examples include iron salts (for example iron sulphate), itraconazole (Sporanox), and ketoconazole (Nizoral, Extina, Xolegel, Kuric).

Dosage and administration

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD): The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 or 40 mg b.i.d. for up to 12 weeks

Drug/Food Interactions

- Avoid alcohol.
- Limit caffeine intake.
- Take without regard to meals, food may slightly increase the product's bioavailability.

Storage: It should be stored in well closed, light resistant container.

Uses

Famotidine is used to treat ulcers of the stomach or intestines. It may be used to prevent intestinal ulcers from returning after treatment. This medication is also used to treat certain stomach and throat problems caused by too much acid

4.3 POLYMER PROFILE

4.3.1 Microcrystalline cellulose [36]

Synonyms

Potato starch, Wheat starch, Corn starch, Rice starch, Cornstarch, Starch, potato, Clearjel, Supertah, Keestar, Maizena, Maranta, Melojel, Starch, wheat, Starken, Amylum, Genvis, Meluna, Trogum, Starch, corn, Amyla

Chemical Structure

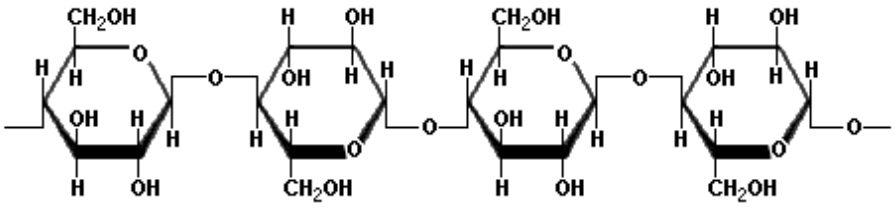


Fig 4.3. Structure of Micro crystalline cellulose

IUPAC Name

5-[3,4-dihydroxy-6-(hydroxymethyl)-5-methoxyoxan-2-yl]oxy-6-[[3,4-dihydroxy-6-(hydroxymethyl)-5-methoxyoxan-2-yl]oxymethyl]-2-[4,5-dihydroxy-2-(hydroxymethyl)-6-methyloxan-3-yl]oxyoxane-3,4-diol

Molecular Formula

$C_{27}H_{48}O_{20}$

Molecular Weight

692.658020 [g/mol]

Description

Microcrystalline cellulose is refined wood pulp. It is a white, free-flowing powder.

Solublity

The products do not dissolve in water, dilute acid and common organic solvent. They partly dissolve in dilute alkali and swell in it.

Incompatibilities

It has been reported that the degradation rate of enalapril maleate was accelerated by in the presence of MCC. The MCC appeared to reduce the apparent heat of fusion of the enalapril maleate.

Isosorbide mononitrate, a nitrooxy dioxabicyclic compound used for treatment of angina pectoris showed an interaction with cellulose acetate and MCC as evidenced by DSC, IST and HPLC studies.

Packing and Storage

The products are packed in composite paper sacks lined with polyethylene film bag. The net weight is 10kg or 25kg per sack. The products shall be stored in sealed container and kept in cool, dark and drying place.

Applications

Microcrystalline cellulose is a commonly used excipient in the pharmaceutical industry.It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly. Microcrystalline cellulose is the same as cellulose, except that it meets USP standards.It is also found as stabilizer, texture modifier, or suspending agent among other uses.

4.3.2 Cross Povidone[37]

Synonyms

E1201,Kollidon,Plasdone,poly[1-(2-oxo-1-pyrrolidinyl)ethylene],polyvidone,polyvinyl pyrrolidone, 1-vinyl-2-pyrrolidinone polymer.

Chemical structure

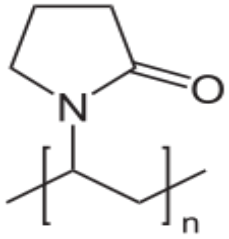


Fig 4.4. Structure of Povidone

IUPAC Name

1-Ethenyl-2-pyrrolidone

Empirical Formula

$(C_6H_9NO)_n$

Molecular Weight

2500 to 3000.

Description

Povidine occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Functional Category

Disintegrant; dissolution aid; suspending agent ; tablet binder.

Incompatibilities

Pharmaceutical Excipients 2215 Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin and other compounds . The efficacy of some preservatives e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

Stability and Storage conditions

Povidone darkens to some extent on heating at 150^{o}C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130^{o} C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hydroscopic, it should be stored in an airtight container in a cool, dry place.

Applications

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation process. 2,3 Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions.Povidone is used as a Solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. 4-6 Povidone solutions may also be used as coating agents.

4.3.3 Sodium Starch Glycolate[38]

Synonyms

Carboxymethyl starch sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Structure

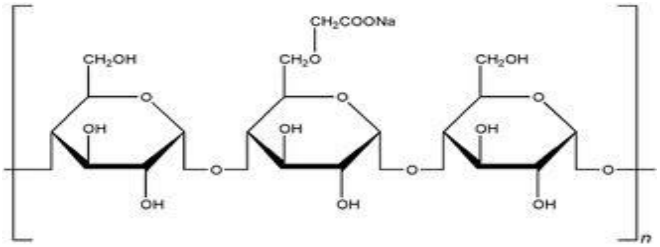


Fig 4.5. Structure of Sodium Starch Glycolate

IUPAC name

(2R,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[(2R,3S,4R,5R,6S)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxyoxane-3,4,5-triol

Molecular Formula

$C_{12}H_{22}O_{11}$

Molecular Weight

342.296480 [g/mol]

Description

It is a white to off-white, tasteless, odorless, relatively free flowing powder.

Solubility

It is very hygroscopic,in water it gives a translucent suspension ,insoluble in organic solvents.

Incompatibilities

Sodium starch glycolate is incompatible with 'clenbuterol' which is a bronchodilator.

Packaging and storage

Preserve in well-closed containers,preferably protected from wide variations in temperature and humidity,which may cause caking.

Applications

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.It is recommended to use in tablets prepared by either direct-compression or wet-granulation process.

The recommended concentration in a formulation is 2-8% with the optimum concentration about 4% although in many cases 2% is sufficient .Disintegration occurs by rapid and enormous swelling.

4.3.4 Lactose[39]

Synonyms

Anhydrous Lactose NF 60 M ; Anhydrous Lactose NF Direct Tab letting ; Lacto press Anhydrous; Lactosum; Milk Sugar ; Pharmatose DCL-21; Pharmatose DCL-22; Saccharum Latis; Super-tab Anhydrous.

Chemical structure

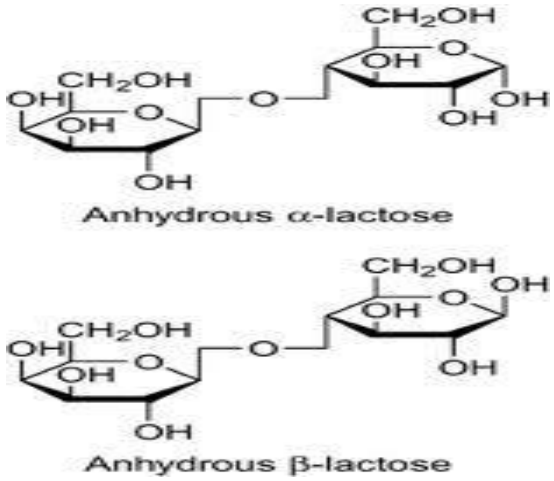


Fig 4.6. Structure of anhydrous α and β lactose

IUPAC name

O-β-D-galacto pyranosyl-(1,4)-β-D-gluco pyranose

Molecular formula

$C_{12}H_{22}0_{11}$

Molecular weight

342.30.

Description

Lactose occurs as a white to off-white crystalline particles or powder.

Solubility

Soluble in water, sparingly soluble in ethanol and ether.

Functional category

Binding agents **;** directly compression vehicle; Lyophilization aid; tablet and capsule filler.

Incompatibilities

Lactose is incompatible with strong oxidizers. When mixtures containing a hydrophobic Leukotrienes antagonist and hydrous lactose were stored for 6 weeks at 40^{o}c and 75% RH, mixture containing anhydrous lactose showed greater moisture uptake and drug degradation.

Stability and storage conditions

Lactose may develop a brown coloration on storage, the reaction accelerated by warm, damp conditions. At 80% RH and 80^{o}c tablets containing anhydrous lactose have been shown to expand 1.2 times after one day. It should be stored in a well-closed container in a cool, dry place.

Applications

Anhydrous lactose is widely used in direct compression vehicle in tablet. It can also be used with the moisture-sensitive drugs due to its low-moisture content.

4.3.5 Croscarmellose Sodium[40]

Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium, Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical structure

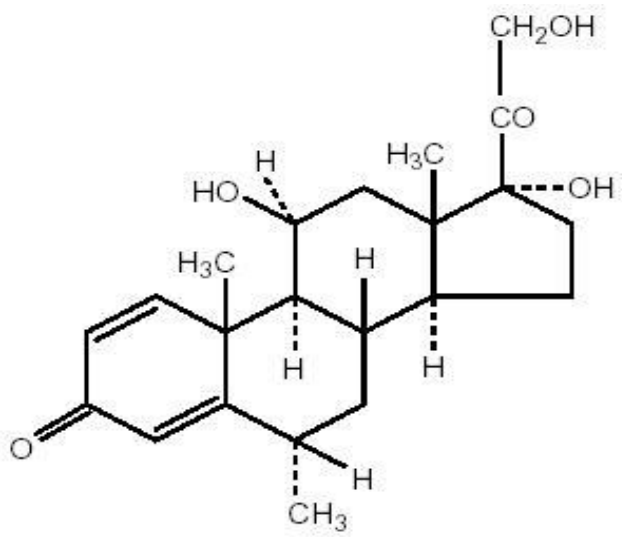


Fig 4.7 Structure of Croscarmellose Sodium

IUPAC Name

Acetic acid,2,3,4,5,6-pentahydroxy hexanal

Empirical Formula

$NaC_6H_7O_6$

Molecular Weight

198

Description

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Solubility

Insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Functional Category

Tablet and capsule disintegrant

Incompatibilities

The efficacy of disintegrates, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Application in Pharmaceutical Formulation or Technology

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra-and extragranularly) so that the wicking and swelling ability of the disintegrate is best utilized.Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2%w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

4.3.6 Magnesium Stearate[41]

Synonyms

Dibasic magnesium stearate, magnesium distearate, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid.

Chemical structure

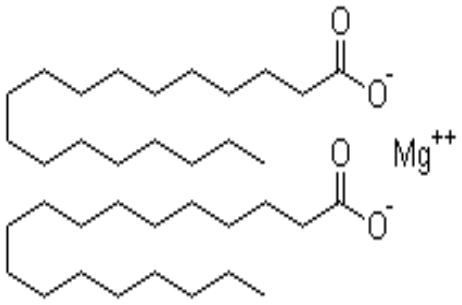


Fig 4.8.Structure of Magnesium Stearate

IUPAC name

Magnesium octadecanoate

Chemical Formula

$C_{36}H_{70}MgO_4$

Molecular weight

591.24

Description

It occurs as a white to off-white powder and odourless.

Solubility

It is not soluble in water .Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95%).

Functional category

It is used as diluent and lubricating agent.

Incompatabilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Stability and storage conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Applications

Magnesium stearate is often used a diluent in the manufacture of medical tablets, capsules and powder. In this regard, the substance is also useful, because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets.

5. METHODOLOGY

Table 5.1 List of chemicals used in this present work

Chemicals	**Source/manufacturer**
Aceclofenac	Madras Pharmaceuticals Ltd, Chennai
Famotidine	Madras Pharmaceuticals Ltd, Chennai
HPMC K_4M	Drugs India, Hyderabad
MCC	Drugs India, Hyderabad
PVP-K_{30}	Drugs India, Hyderabad
Isopropyl Alcohol	SDFCL , Mumbai
Talc	SDFCL , Mumbai
Magnesium Stearate	SDFCL , Mumbai
Starch	SDFCL , Mumbai
Lactose	SDFCL , Mumbai
Crosscarmellose sodium	SDFCL , Mumbai
Sodium starch glycolate	SDFCL , Mumbai

Table 5.2 List of instruments/equipments used.

Equipments	Modified/Manufacturer
Electronic balance	Wensar weighing scales Ltd, Mod.No:PGB200
Double rotary tablet compression machine	Karunavati Pvt Ltd., Rajasthan (RIMEK minipress)
Hardness tester, Pfizer	Mitutoyo South Asia Pvt Ltd., New Delhi
Friabilator	Roche Friabilator
pH meter	Shankar Scientific, Chennai
Hot air oven	Model MP-1 Plus Susima Dharma
Dissolution Apparatus	Lab india disso-2000
Double beam spectrophotometer	Schimadzu 1700 UV-Vis Double beam spectrophotometer,Shimadzu Scientific Instruments, Japan
FT-IR Spectrophotometer	Shimadzu Scientific Instruments, Japan
Differential Scanning Colorimeter	Q10 TA systems, USA

5.1 Construction of calibration curve for Aceclofenac and Famotidine

5.1.1 Stock for standard curve

Accurately weighed 100mg of aceclofenac in 100 mL of volumetric flask was dissolved completely with1/ 3 volume of pH 7.4 phosphate buffer and volume made up with the same.

From above stock solution 1mL was taken into 100mL volumetric flask and diluted with pH 7.4 phosphate buffer in order to get 5, 10, 15 & 20µg/ mL concentration and absorbance was read at 273nm.

The same method was adopted for the construction of calibration curve of famotidine and absorbance was at 260 nm.

5.2 Preformulation studies

Preformulation can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. The overall objective of Preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. The following data must be considered,

- Loss on drying
- Solubility studies
- Micromeritic properties
- pH studies
- Compatibility studies

5.2.1 Loss on drying studies

The Loss on Drying Test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. Dry a weighing bottle for about 30 minutes under 100-105^{0}c, allow to cool it in a desiccators if heated, and weigh it accurately. Place 1 to 2g of acclofenac into the weighing bottle spread the sample so that the layer is not thicker than 5mm, and weighs it accurately. Place the bottle in the drying oven, remove the stopper (placing it nearby), dry under 105^{0}c for 3 hours, stopper again, take the bottle out of the oven, and weigh it again. Allow to cool it in a desiccator, and weigh it accurately. Same procedure was also done with famotidine as a sample.

$$\text{LOD (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5.2.2 Solubility studies of aceclofenac drug and famotidine drug

An excess quantity of aceclofenac drug and famotidine drugs were taken separately and added in 10ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed.

5.2.3 Micromeritic properties evaluation

Angle of repose of aceclofenac and famotidine were assessed by the fixed funnel method. A known amount of drug was allowed to flow through a funnel fixed at a constant height (h) and the height and diameter (2r) of the pile of powder were measured to calculate the angle of repose as $\theta = \tan^{-1}$ (h/r). The loose bulk density (LBD) and tapped bulk density (TBD) of aceclofenac

and famotidine were determined using a bulk density test apparatus. Carr's index and Hausner's ratios were calculated using LBD and TBD values. Then again the micromeritic properties of these two drugs were checked with the addition of various fillers.

5. 2.3.1 Flow Properties[42-45]

5. 2.3.1.1 Angle of repose (θ)

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Procedure

Angle of repose was determined using funnel method. Pour the powder on to the surface of funnel from certain height(h) . Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken as radius(r).By using this Angle of repose was calculated using following formula:

$$\text{Angle of repose}(\theta)=\tan^{-1}(h/r)$$

Where,

h = height of a pile

r = radius of pile base.

Acceptable range for angle of repose is 20^{θ} to 40^{θ}.

5. 2.3.1.2 Bulk density

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder.

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 18 and 10 mg of pure drug was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (D_b) was calculated in g/ml by the formula:

$$D_b = M/Vo$$

Where,

M = mass of powder taken

Vo= unsettled apparent volume

Limits

It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

5. 2.3.1.3. Tapped density

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 10 mg of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the

initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated. Tapping was continued for additional 1250 tap if the difference is more than 2%. This volume was noted as, the final tapped volume (Vo). The tapped density (Dt) was calculated in g/ml by the formula:

$$Dt = M/ Vo$$

Where,

M = Weight of sample powder

Vo = final tapped volume

5. 2.3.1.4. Carr's index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down.

The formula for Carr's index is as below equation

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped Density}} \times 100$$

Tab 5.3 Compressibility index

% Compressibility	Flow ability
5-15	Excellent
12-16	Good
18-21	Fair- Possible
23-35	Poor
33-38	Very poor
<40	Very, Very poor

5. 2.3.1.5. Compressibility Index (% Compressibility)

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index was calculated using following equation:

$$CI\ (\%) = [(D_t - D_b)/D_t] \times 100$$

Where,

D_t = Tapped density

D_b = Bulk density

5. 2.3.1.6. Hausner's Ratio

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula:

$$\text{Hausner Ratio} = D_t/D_b$$

Where,

D_t = tapped density

D_b = bulk density

Tab 5.4. Standard limits corresponding to powder flow and packaging characteristics

Angle of repose(θ)	Compressibility Index (%)	Hausner's ratio	Flow properties
25-30	<10	1.00-1.11	Excellent
31-35	11-15	1.12-1.18	Good
36-40	16-20	1.19-1.25	Fair
41-45	21-25	1.26-1.34	Passable
46-55	26-31	1.35-1.45	Poor
56-65	32-37	1.46-1.59	Very poor
> 66	>38	>1.6	Very very poor

5.2.4 pH Studies

The pH studies were done for both aceclofenac and famotidine which were dissolved in their suitable solvent, determined with the help of pH potentiometer

5.2.5 Compatibility studies

5.2.5.1. FT-IR Study

Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a shimadzu FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

5.2.5.2. Differential scanning Calorimetry (DSC)

DSC thermo grams of drug and excipients were recorded using a differential scanning calorimeter (Q10 TA systems, USA). About 5mg of sample were crimped in a standard aluminium pan and heated in a temperature range of 50^0C to 450^0C at a heating rate of 10^0C per minute in nitrogen atmosphere**.**

5.3 FORMULATION OF BILAYERED FLOATING TABLETS

5.3.1 Formulation of immediate release (IR) tablets by direct compression

The inner core tablets were prepared by using direct compression method as per formulation variable shown in Tab5.5. Powder mixtures of aceclofenac, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol), Sodium starch glycolate, crospovidone, lactose monohydrate ingredients were dry blended for 20 min followed by addition of magnesium stearate. The mixtures were then further blended for 10 min. 181 mg of resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton, with a 9mm punch and die to obtain the core tablet.

Tab.5.5 Composition of various formulations of immediate release layer

Compositions	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac(mg)	100	100	100	100	100	100	100	100
Cross povidone(mg)	5	7.5	12.5					
MCC(mg)				5	7.5	12.5		
Sodium starch glycolate. (mg)							5	7.5
Lactose.(mg)	68.5	66.0	61	68.5	66.0	61	68.5	66.0
Purified talc.(mg)	5	5	5	5	5	5	5	5
Magnesium stereate(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

5.3.2 Preparation of bi-layered floating tablets (wet granulation)

Bilayered tablet of sustained release famotidine and immediate release aceclofenac were prepared through wet granulation method according to the composition. Various steps (sieving, dry mixing, binder solution preparation, granulation and subsequent drying)were involved in wet granulation process.

Wet granulation Procedure

Granulation of famotidine

Step:1

- Sieving

The active ingredient Famotidine drug was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Step:2

- Dry mixing

Famotidine, HPMC K100M, HPMC K4M, MCC were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Step:3

- Preparation of binder solution
  - PVP-K_{30}
  - IPA

Weigh 9mg of PVP K-30 accurately and it is mixed with IPA to form a paste is used as binder solution and kept separately.

Step:4

- Granulation

The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules.

Step:5

- Drying

Then the wet granules were dried in trays and pass the air for drying since the IPA is corrosive and also get evaporated quickly. So air drying is only suitable for drying, samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content.

Step:6

- Sieving

The dried materials were passed through the sieve #20

Tab.5.6 Composition of various formulations of sustained release layer

compositions	Formulation code							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Famotidine (mg)	40	40	40	40	40	40	40	40
HPMC(mg)	87.5	105	122.5	140	-	-	-	-
Guar gum(mg)	-	-	-	-	87.5	105	122.5	140
$NaHC0_3$(mg)	70	70	70	70	70	70	70	70
PVP(mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Lactose monohydrate(mg)	131.5	114	96.5	79	96.5	61.5	44	26.5
Magnesium stearate(mg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
IPA	q.s.	q.s.	q.s	q.s.	q.s.	q.s.	q.s	q.s.

5.3.3 Lubrication and compression of bilayered tablets

Magnesium stearate, and talc were weighed and they were passed through sieve#20.Then mixed with dried granules of Famotidine in a polybag for 5minutes to get a uniform blend. Then the lubricated granules of Famotidine and lubricated granules of Aceclofenac drug were added in the separate hopper in double rotary punching machine and compressed into bilayered tablets using 18.6 X 9mm caplet shape punches, at weight of 531mg each.

5.4 POST COMPRESSION EVALUATION OF BILAYERED TABLETS

5.4.1 Physical appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing.

5.4.2 Weight variation

Twenty tablets were randomly selected from each batch weighed individually. Calculate the average weight and compare the individual weight to the average weight.

Tab 5.7 Specifications for Weight variation of Tablets

AVERAGE WEIGHT OF TABLETS(mg)	**% DIFFERENCE**
130 or less	10%
130 or 324	7.5%
> 324	5%

5.4.3 Thickness

Five tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of screw gauge. The average thickness was calculated.

5.4.4 Hardness

Hardness was measured by using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated in terms of kg/cm.

5.4.5 Friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

If the tablet weight is >650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in Roche Friabilator for 100 revolutions at 25 rpm. The tablets were de-dusted and reweighed. The %friability should be not more than 1% w/w of the tablets is being tested.

The % friability is expressed as the loss of weight and is calculated by formula

$$\%F = \{(W - W_0)/W\} \times 100$$

Where,

% F	=	Friability of tablets in percent.
W	=	Initial Wight of tablets.
W_O	=	Final weight of tablets.

5.4.6 Wetting time

Wetting time of dosage form is related to the contact angle. A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. Tablet was kept on the paper and the time for complete wetting was measured. The mean ± SD values were calculated accordingly.

5.4.7 Drug content

For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 7.4 in a volumetric flask. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically for each drugs against blank. Drug content was calculated using standard curve.

5.4.8 Disintegration time

Disintegration time is the time required for a tablet to break up into granules of specified size (or smaller), under carefully specified test conditions. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm length and 2.15 mm

in diameter the bottom of which consists of a 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900 ml which is maintained at 37±2°C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet.

5.4.9 Dissolution Studies

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

In-vitro release studies for immediate release (IR)

Dissolution rate studies of both the drugs from all formulations were performed using dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of phosphate buffer pH 7.4. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Aceclofenac and Famotidine by measuring absorbance at 273 nm. The dissolution experiments were conducted in triplicate.

In-vitro Dissolution methods for bilayer floating tablets

The release of Aceclofenac and Famotidine from the bilayer floating tablet was accomplished *In-vitro* release study was carried out (USP dissolution test apparatus Type-II Paddle type) using 900 ml of Distilled water with 0.5% SLS a. The paddles are rotated at 50 rpm. The medium was set at 37 ± 0.5^0 C. Aliquot (5 ml) of the solution was collected from the dissolution apparatus

hourly and was replaced with fresh dissolution medium. The withdrawn samples were analyzed by an UV spectrophotometer at 260 nm.

5.5 Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity. Selected formulations were subjected to stability studies as per ICH guidelines at 30ºC/65% RH and 40ºC/75% RH for 45 days. Sample were taken and analyzed at time interval.

Selected formulation were subjected to stability studies as per ICH guidelines sample were taken and analysed at time interval of 15 days for 45 days.

Tab 5.8. Storage conditions for checking the quality of drug product

S.NO	STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
1.	Long term	25ºC + 2ºC/60% RH + 5ºC (or) 30C + 2ºC/65% RH + 5%RH	12 months
2.	Intermediate	30ºC + 2ºC/65% RH + 5%RH	6 months
3.	Accelerated	40ºC + 2ºC/75% RH + 5%RH	6 months

5.6 KINETIC MODELS

Release Kinetics

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release.

To analyses the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order and First order model. In this by comparing the R-values obtained, the best-fit model was selected.

Zero Order Kinetics

This model describes the system where the release rate is independent of the concentration of the dissolved species. Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly assuming that area does not change and no equilibrium conditions are obtained can be represented by the following equation.

$$W_0-Wt=Kt$$

Where,

Wo = Initial amount of drug in pharmaceutical dosage form

Wt = Amount of drug in the dosage form at time t

K = Proportionality constant.

Dividing this equation by Wo and simplifying

$$f_t = kot$$

Where, ft = 1-(Wt/Wo)

which represents the fraction of drug dissolved in time t

Ko= Apparent dissolution rate constant or zero order release constant

The pharmaceutical dosage forms following this profile release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This following relation can in a simple way express this model.

$$Qt = Qo + Kot$$

Where, Qt= Amount of drug dissolved in time t,

Qo = Initial amount of drug in the solution and

Ko = Zero order release constant.

First Order Kinetics

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

To study the first order release rate kinetics, the release rate data were fitted to the following equation.

$$\log Q_t = \log Q_o + K_1 t / 2.303$$

Where, Q_t = Amount of drug released in time t,

Q_o = Initial amount of drug in the solution and

K_1 = First order release constant.

The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way that the amount of drug released by unit of time diminished.

Higuchi Model

A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies as formula:

$$Q = k_2 t^{1/2}$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant

In higuchi model, a plot of % drug released versus square root of time is linear.

6. RESULTS AND DISCUSSION

6.1 Construction of calibration curve for Aceclofenac and Famotidine

6.1.1Standard curve for aceclofenac in pH 7.4 buffer

Tab 6.1 Standard plot of aceclofenac

Concentration (µg/ml)	Absorbance
0	0
5	0.1978
10	0.3956
15	0.5657
20	0.7359

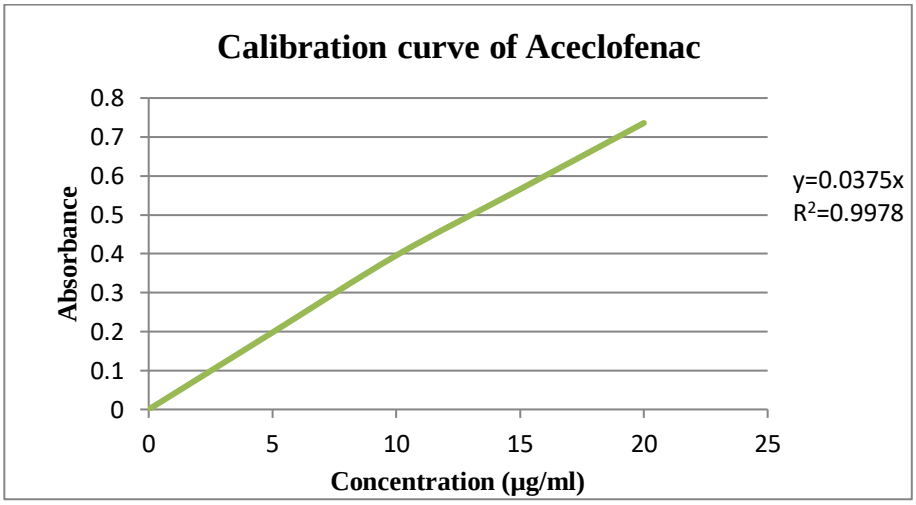


Fig 6.1 Standard plot of aceclofenac in pH 7.4 buffer

6.1.2 Calibration curve for famotidine

Table 6.2 Standard plot of famotidine

Concentration (µg/ml)	Absorbance
0	0
5	0.212
10	0.424
15	0.636
20	0.884

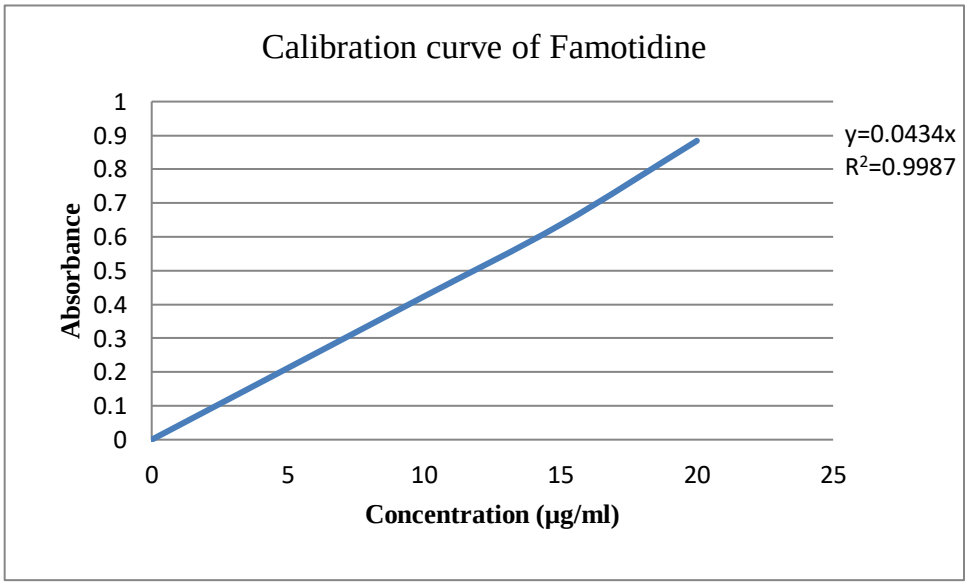


Fig 6.2 Standard plot of famotidine

6.2 Preformulation Studies

Tab 6.3. Solubility studies of aceclofenac and famotidine

Solvent	Aceclofenac	Famotidine
Water	Soluble	Soluble
Methanol	Highly Soluble	Highly Soluble
Ethanol	Sparingly soluble	Sparingly soluble
Chloroform	Insoluble	Soluble
DMSO	Soluble	Soluble
0.1N Hcl	Soluble	Soluble
pH 6.8 buffer	Highly Soluble	Soluble
pH7.4 buffer	Soluble	Sparingly soluble

The availability of literature on solubility profile of aceclofenac and famotidine indicates that the drugs were freely soluble in methanol and water. And also it tells that both drugs solubility increases by increasing the pH nearly alkaline. This was confirmed by observing the solubility studies of aceclofenac, famotidine hemi hydrate practically. However, pH 6.8 phosphate buffer may be suitable for dissolution studies as sufficient solubility was attained at this pH for both the drugs. But on the other hand, the present formulation contains sustained release layer and

immediate release layer too; it would be more meaningful to use both acidic and alkaline media for dissolution studies.

6.3 Micromeritic evaluation

Tab 6.4 Flow properties of aceclofenac IR layer granules

Formulation code	Angle of repose (θ)	Bulk density gm/cc	Tapped density gm/cc	Carr's index %	Hausner's ratio %
F1	21.04± 0.14	0.304± 0.004	0.351± .05	17.0 ± 0.11	1.17 ±0.06
F2	21.09± 0.08	0.317± 0.002	0.367±0.08	18.1 ± 0.09	1.19 ±0.03
F3	21.46± 0.15	0.310± 0.007	0.360±0.01	18.7 ± 0.07	1.21 ±0.02
F4	24.88± 0.13	0.318± 0.007	0.378±.06	19.5 ± 0.05	1.19 ±0.04
F5	24.23± 0.10	0.294± 0.005	0.346±0.04	19.5 ± 0.10	1.20 ±0.05
F6	24.09± 0.10	0.307± 0.004	0.360±0.02	20 ± 0.10	1.24 ±0.07
F7	24.78± 0.12	0.311± 0.04	0.368±0.05	19.1 ± 0.11	1.22 ±0.07
F8	25.56± 0.18	0.265± 0.06	0.312±0.03	20 ± 0.09	1.23 ±0.02

Tab 6.5 Flow properties of famotidine SR layer granules

Formulation code	Angle of repose (θ)	Bulk density gm/cc	Tapped density gm/cc	Carr's index %	Hausner's ratio %
F1	21.04± 0.14	0.304± 0.007	0.351± .03	13.41± 0.09	1.15 ±0.05
F2	21.09± 0.08	0.317± 0.06	0.367±0.05	13.63± 0.05	1.18 ±0.07
F3	21.46± 0.15	0.310± 0.04	0.360±0.08	13.89± 0.10	1.20 ±0.06
F4	$24^0$88± 0.13	0.318± 0.005	0.378±0.01	15.87± 0.09	1.19 ±0.04
F5	24.23± 0.10	0.294± 0.004	0.346±0.06	15.02± 0.11	1.22 ±0.05
F6	24.09± 0.10	0.307± 0.002	0.360±0.04	14.72± 0.07	1.24 ±0.03
F7	24.78± 0.12	0.311± 0.007	0.368±0.02	15.21± 0.10	1.22 ±0.07
F8	25.56± 0.18	0.365± 0.06	0.312±0.05	15.06± 0.11	1.24 ±0.02

6.4 pH studies

The pH value of aceclofenac is 7.4. The pH value of famotidine is 6.7 So, both the drugs were well soluble in pH 5and 7 and have more unionized nature in this pH.

6.5 Compatibility studies

FT-IR spectroscopy was employed to ascertain the compatibility of drugs with polymers. The individual drug and drug with polymers were separately scanned. Both the spectra were compared for confirmation of common principal peaks. 3505.03, 3400.28, cm-1 for NH stretching of famotidine and peaks at 1598.44 cm-1 wave number were due to C-C stretching in aliphatic chain and prominent peaks at 1728 cm-1and 1282-1320 cm-1 were due to C=O stretching of aceclofenac.

Therefore Aceclofenac and famotidine with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. DSC peaks are observed their corresponding meting points and the same were also shown in formulation, hence it indicates that no interaction of drugs and polymers in the formulation.

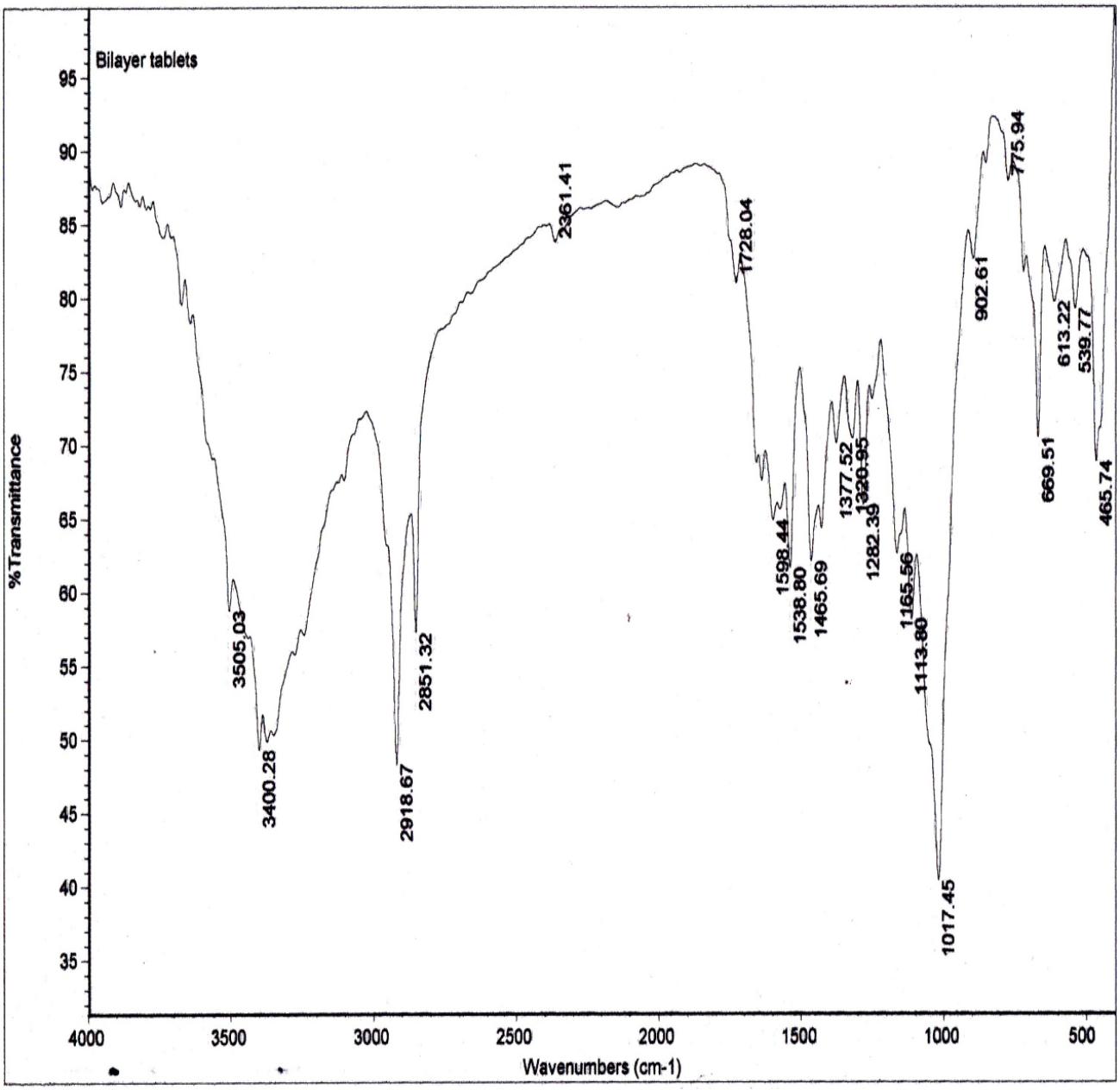


Fig 6.3 FTIR Spectra of bilayer formulation of aceclofenac and famotidine

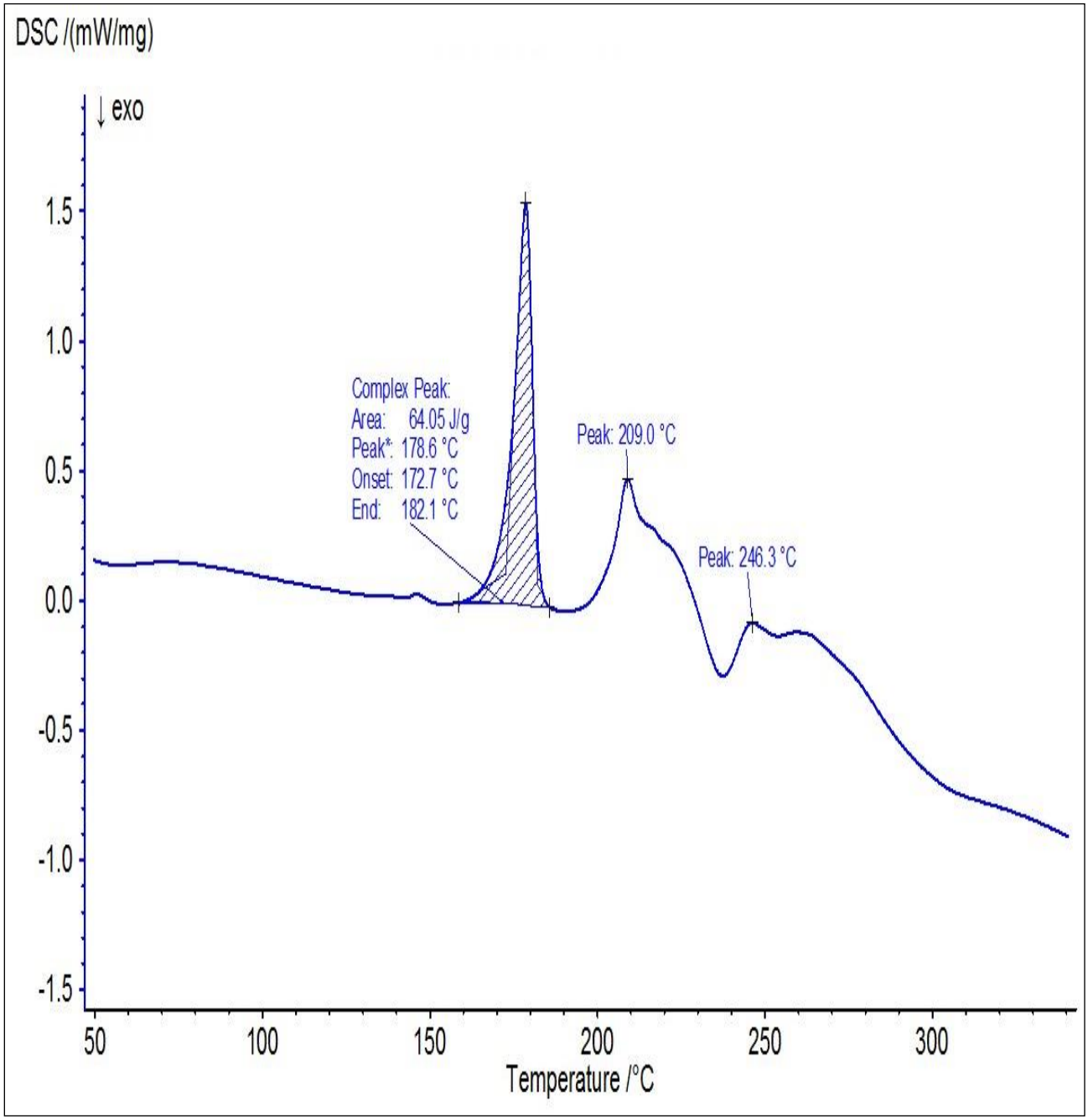


Fig 6.4 DSC thermogram of aceclofenac pure

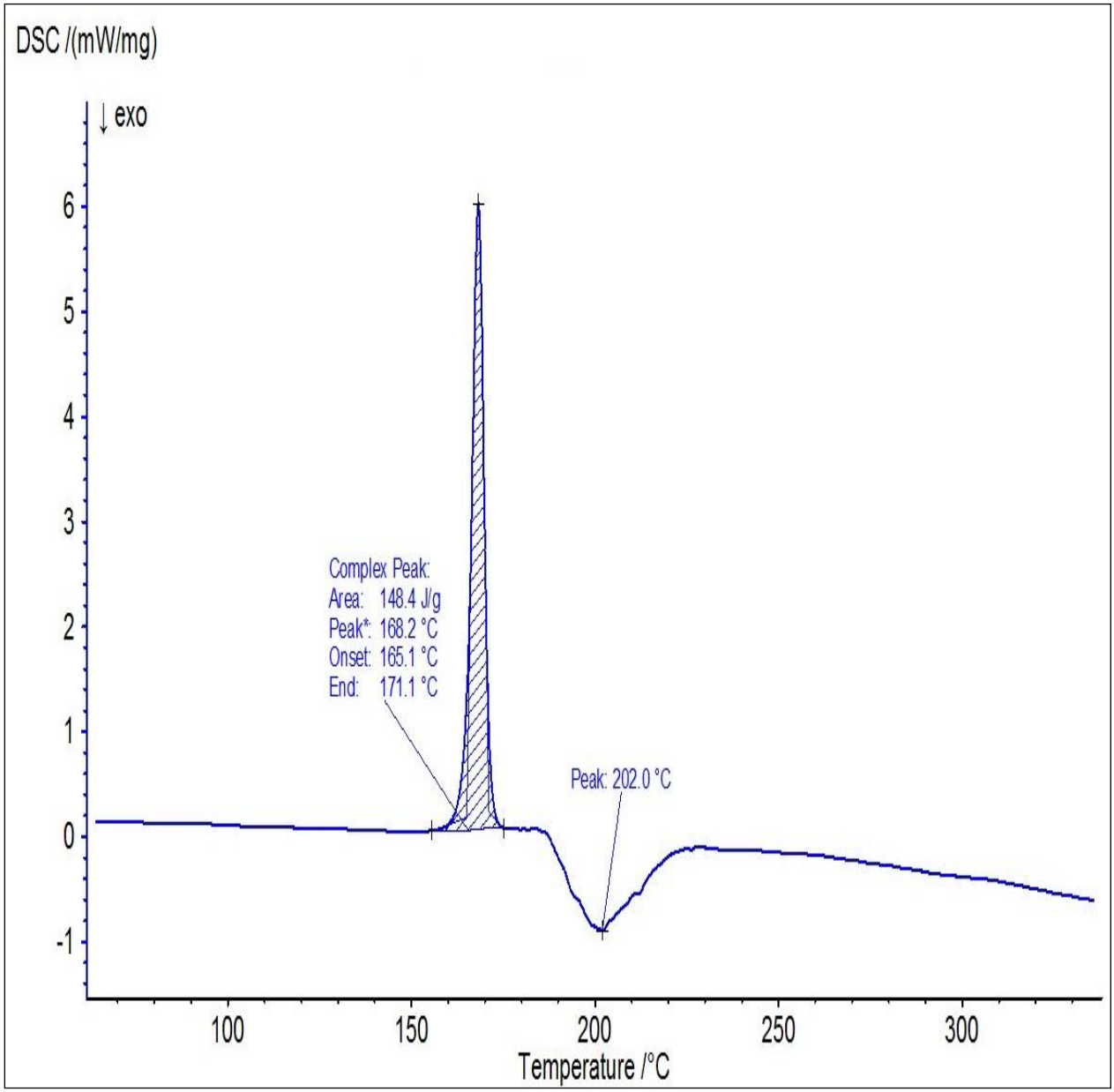


Fig 6.5 DSC thermogram of famotidine pure

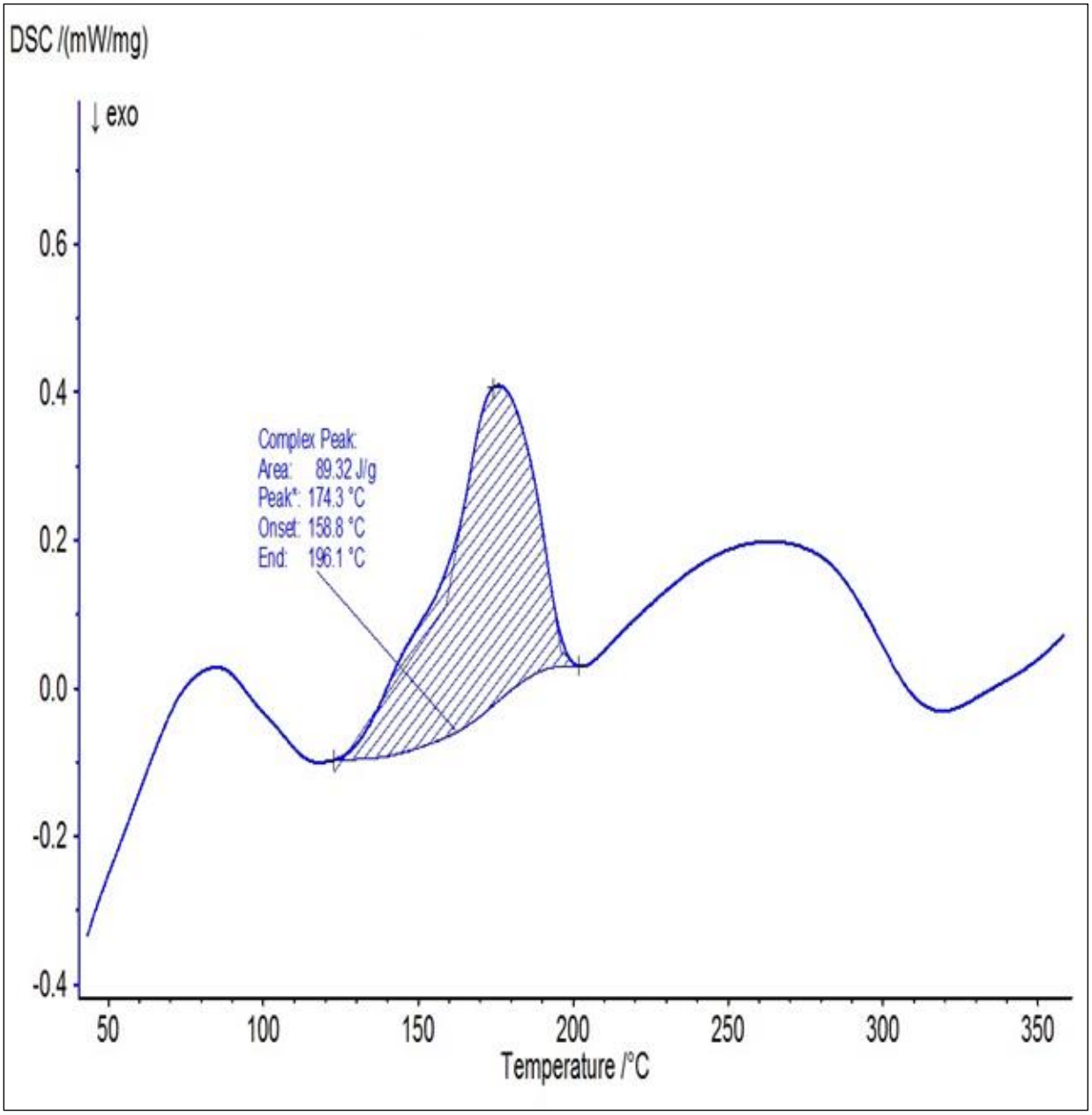


Fig 6.6 DSC thermogram physical mixture of famotidine and excipients

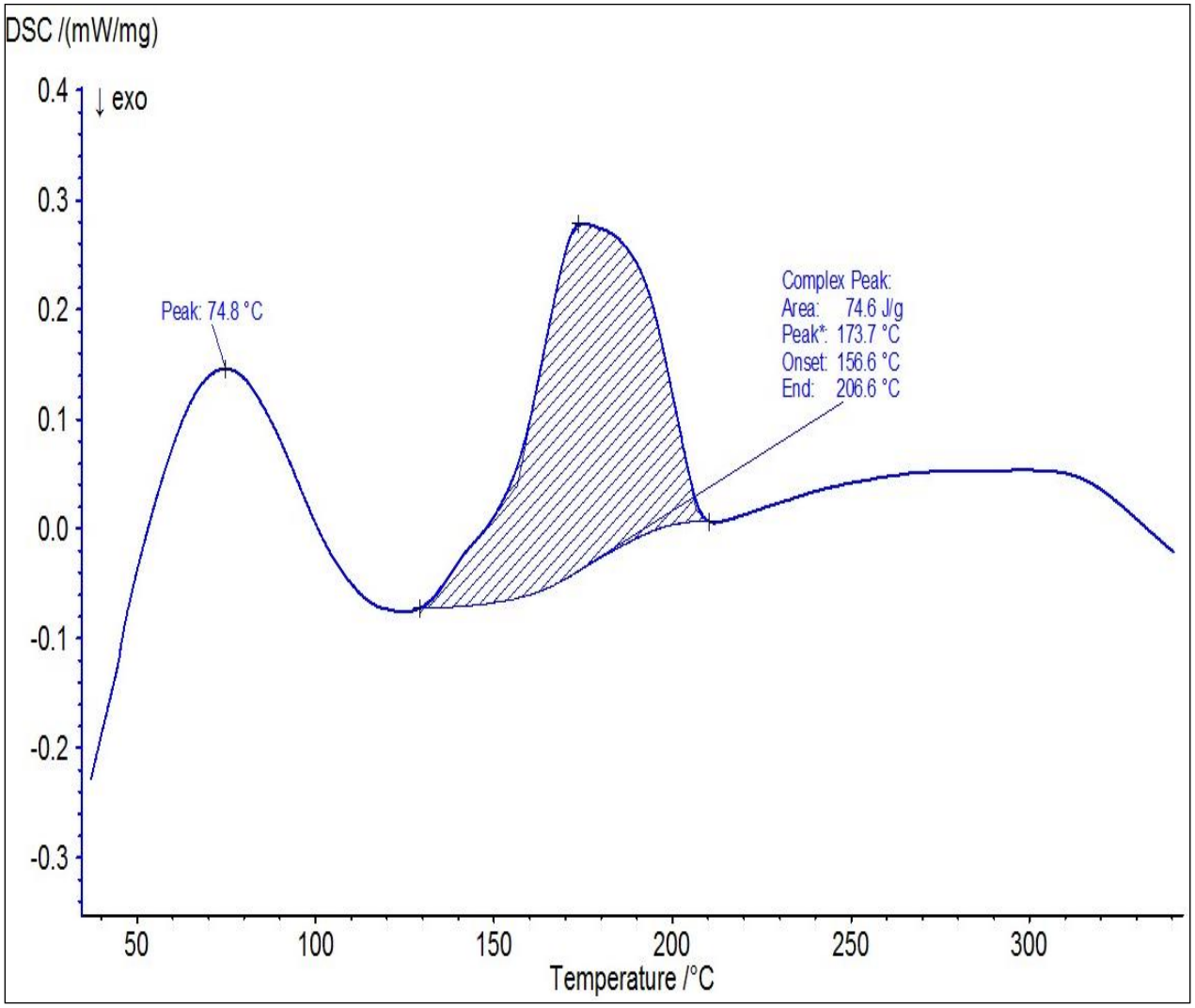


Fig 6.7 DSC of formulation

6.6 POST COMPRESSION EVALUATION

Tab 6.6 Physicochemical evaluations of bi-layered tablets

Formulation	Avg. Weight(Mean ±S.D)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	540.4±0.48	4.5±0.055	2.4±0.32	1.435	98.70
F2	532.6±0.74	4.7±0.010	6.4±0.29	0.492	99.25
F3	534.7±0.62	4.1±0.017	6.9±0.24	0.501	99.42
F4	545.4±0.47	4.3±0.012	2.3±0.41	2.963	97.52
F5	541.2±0.23	4.5±0.072	6.1±0.32	0.478	98.24
F6	531.9±0.32	4.9±0.021	6.8±0.32	0.242	98.63
F7	528.1±0.54	4.7±0.054	5.8±0.39	0.414	98.15
F8	539.8±0.37	5.0±0.034	6.4±0.42	0.417	99.42

6.7 DISSOLUTION STUDIES

Tab 6.7 Cumulative percentage of drug release of famotidine SR layer for Formulation F1-F8 formulated with HPMC and Guar Gum of different concentrations

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	36 ±0.3	30±0.56	27±0.24	19±0.44	16±0.24	20±0.64	11±0.54	10±0.25
2	52±0.33	45±0.34	42±0.34	32±0.54	29±0.22	31±0.24	19±0.61	19±0.84
3	59±0.45	59±0.75	49±0.15	42±0.24	44±0.55	43±0.29	26±0.54	29±0.94
4	68±0.52	69±0.25	58±0.55	54±0.35	50±0.14	49±0.34	38±0.34	46±0.56
5	89±0.23	78±0.32	66±0.25	61±0.21	59±0.85	60±0.21	45±0.61	58±0.75
6	95±0.66	89±0.43	80±0.88	68±0.55	69±0.24	72±0.28	58±0.21	67±0.87
8	-	97±0.55	98±0.75	83±0.61	82±0.78	86±0.95	67±0.61	73±0.56
10	-	-	-	98.3±0.24	95±0.94	-	75±0.54	79±0.21

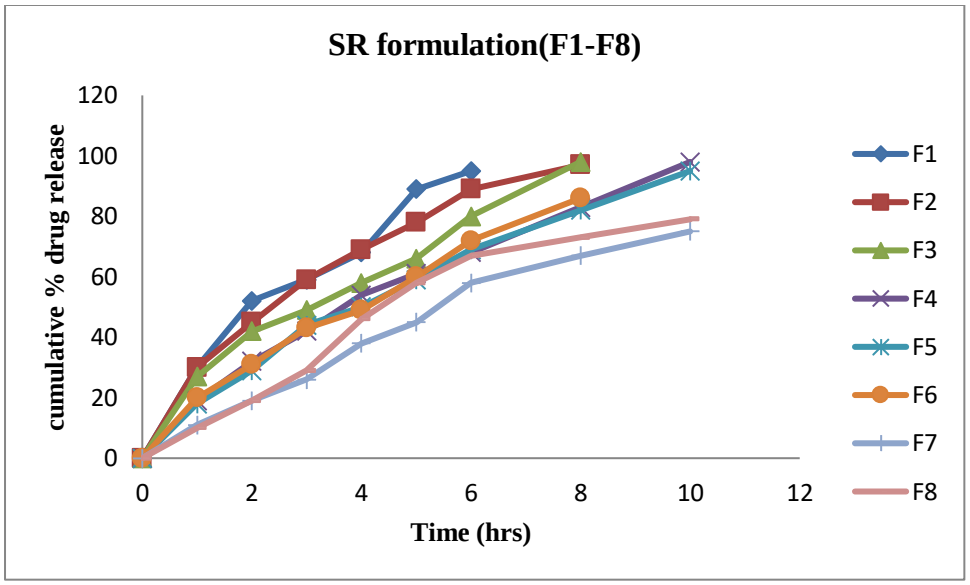


Fig 6.8 Graph representing Cumulative % Drug Release of drug SR layer of Trials F1-F8 formulations

Tab 6.8 Cumulative percentage of drug Release of aceclofenac IR layer of F1-F8 formulated with different disintegrants

TIME (min)	F1	F2	F3	F4	F5	F6	F7	F8
5	15±0.25	18±0.66	20±0.34	13±0.64	18±0.55	23±0.25	15±0.54	14±0.34
10	24±0.34	29±0.84	34±0.64	23±0.51	29±0.42	36±0.45	22±0.61	24±0.61
15	30±0.61	40±0.55	43±0.51	32±0.84	39±0.31	43±0.31	31±0.03	33±0.01
20	39±0.24	48±0.45	52±0.35	42±0.94	46±0.51	52±0.61	40±0.61	42±0.35
30	48±0.84	63±0.87	69±0.84	50±0.61	68±0.94	73±0.94	49±0.02	53±0.21
45	68±0.55	77±0.95	80±0.22	67±0.37	81±0.64	90±0.21	59±0.21	65±0.02
60	80±0.64	84±0.25	92±0.34	80±0.55	89±0.34	101±0.04	72±0.84	78±0.80

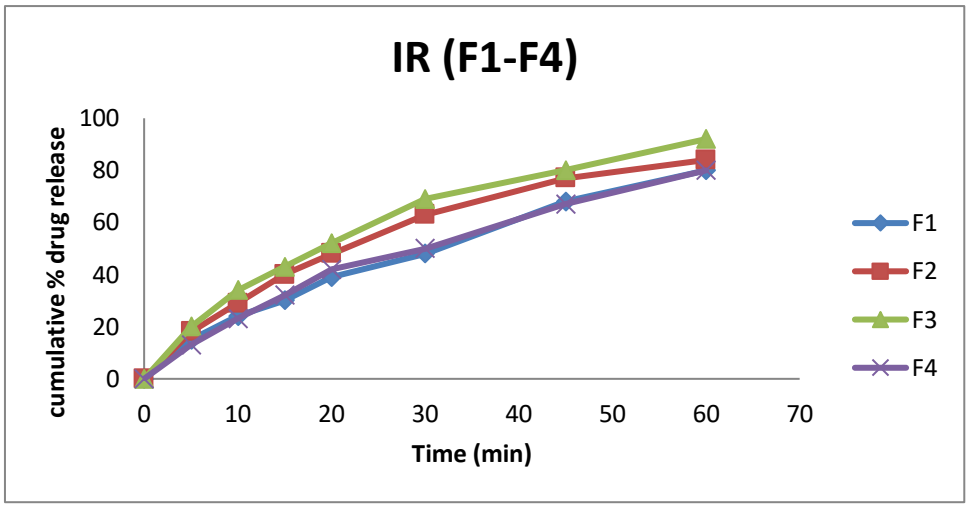


Fig. 6.9(a) Graph representing Cumulative % Drug Release of Model drug IR layer of Trials F1-F4 formulated with different disintegrants within one hour

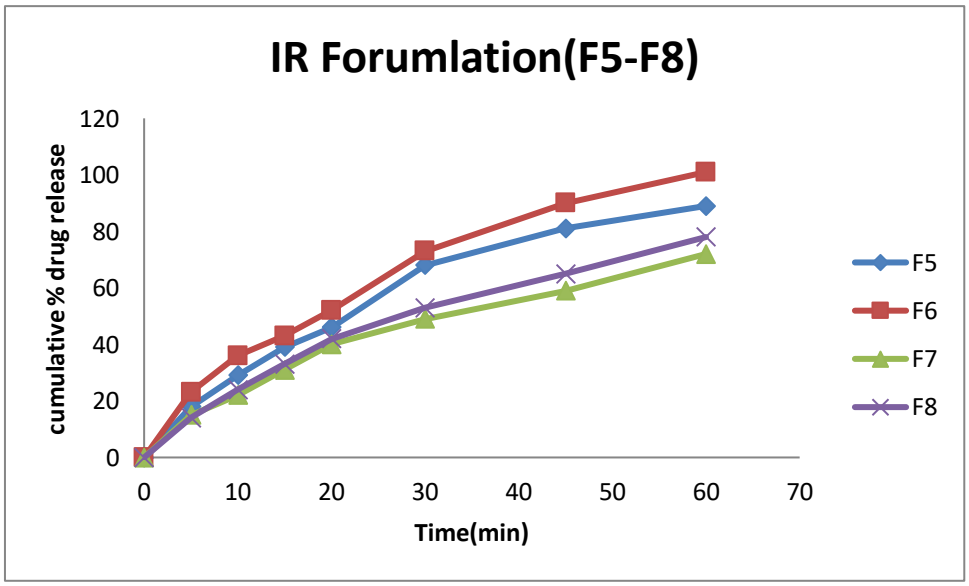


Fig. 6.9(b) Graph representing Cumulative % Drug Release of Model drug IR layer of Trials F5-F8 formulated with different disintegrants within one hour

Tab 6.9 shows kinetics behaviour of different formulations famotidine SR layer of formulations F1-F8

R^2 Regression coefficient								
Kinetic order	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Zero-order	0.910	0.829	0.908	0.928	0.931	0.953	0.966	0.920
First-order	0.913	0.970	0.9610	0.998	0.991	0.976	0.967	0.963
Higuchi	0.974	0.990	0.984	0.968	0.956	0.956	0.872	0.835

Dissolution test

The results of *in-vitro* drug release studies in phosphate buffer (from 3 to 10 hours) are presented in tab 6.7 and Fig.6.8. Initially our aim was to select optimum concentration of HPMC of different grades for SR layer and optimum concentration of Starch (Disintegrant) for IR layer.

Hence the tablets containing,

- SR layer of drug (famotidine) were prepared by altering the concentration of different polymers HPMC and guar gum
- IR layer of drug (aceclofenac) were prepared by altering the concentration of cross povidone, croscarmellose sodium and sodium starch glycolate.

Discussion for *in-vitro* release of drug layer SR

From the table, it was confirmed that the formulations of F1- F8 of SR layer does not fulfill the sustained release theory, In that the HPMC and guar gum were used separately in the formulations, but increasing the polymer concentration, it was clearly identified that the drug release was retarded. And also from the table, it was also confirmed that the formulation made with HPMC (F1 to F3) releases the drug in less amount compared to the formulation made with guar gum (F6 to F8), since its viscosity is somewhat higher than guar gum.

In order to produce optimized formulation, both the Polymers were used together in formulations of remaining trials. Yet the formulation F7 of famotidine SR layer made of both HPMC and guar gum was not attained the sustained release. The formulations F8 was made with same

concentration as that of F3 with little altering in binder concentration. But there was no major change in drug release and also the hardness of the tablet goes beyond the limit.

The next formulation F4 of famotidine SR layer made of HPMC 40(%) and guar gum (20%) sustained the drug release up to 12^{th} hour (not shown in Table) and also the release was similar to that of marketed sample. When the concentration of HPMC and guar gum was again increased for the formulation F5, the drug from the tablet was very hard to release

So formulation F4 made of 140mg of HPMC and 140mg of guar gum was considered as optimized formulation for SR layer.

The drug release kinetic study indicated that the release data was best fitted with first order kinetics. Higuchi equation explains the diffusion controlled release of the drug through SR tablets.

Discussion for *Invitro* release of drug IR layer:

Then for the tablet of IR layer, 8 trials were made. In those trials, the formulation (Trial F6 of aceclofenac layer) made with crosscarmellose sodium 5% (12.5mg) released the drug with in one hour and also has the sufficient hardness and friability than other formulations. So the formula made for formulation F6 of aceclofenac layer was considered as optimized formulation and that formula was used for preparing of famotidine SR layer to produce the Bilayered floating tablet.

6.8 Stability study

The stability study was carried out on optimum formulation F6, and its results reflect that there is no significant change in dissolution profile, drug content and bilayer tablets of the formulation. Hence, it concludes that the tablets from this formulation are stable for the period 3 months at 40 ±2°C.

Tab 6.10 Stability studies of optimized formulation

Parameters	**1st month**	**2nd month**	**3rd month**
Physical appearance	No Change	No Change	No Change
Swelling index	70.51±0.60	69.76±0.60	69.48±0.3
Drug content	98.70±0.47	98.63±0.116	99.43±0.101
In-vitro drug release	95.57±0.53	100.49±0.55	99.43±0.79

All values are expressed as Mean±SD

7. SUMMARY AND CONCLUSION

- ✓ The Bilayered floating tablets containing famotidine SR and aceclofenac IR were successfully prepared by wet granulation method.

- ✓ The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index and drug content

- ✓ The prepared granules also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability and drug content. The optimized formulation contains the average thickness of 5.4±0.042, average hardness of 6.4±0.14, average weight of 600±0.56, friability of 0.021 and 99.72% of drug content.

- ✓ In the 8 trials, the optimized formulation was F4 trial which releases the famotidine in sustained manner similar to the release given by marketed famotidine SR sample i.e., in 1st hour it releases 19 % but the remaining drug release was sustained up to 12 hours and the same formulation which releases the aceclofenac immediately with in an hour since the tablet disintegrated with in 15 minutes.

- ✓ The optimized tablets of formulation F4 were selected for stability studies and they were kept in two different temperatures. The stability studies confirmed that there was no significant difference over a stability testing period.

“Hence it may be summarized that the formulation F4 prepared by wet granulation method might be a perfect and effective formulation for the treatment.

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